
*The Value of Quinidine in Cases of
Auricular Fibrillation and Methods
of Studying the Clinical Reaction*

First Lecture

BY

THOMAS LEWIS

UNIVERSITY COLLEGE HOSPITAL, LONDON, ENGLAND

FROM THE

AMERICAN JOURNAL OF THE MEDICAL SCIENCES

June, 1922, No. 6, vol. clxiii, p. 781

WELLCOME INSTITUTE LIBRARY	
Coll.	welMOmec
Coll.	pam
No.	QV 150
	1 9 22
	L 67v



22500892763

THE VALUE OF QUINIDINE IN CASES OF AURICULAR FIBRILLATION AND METHODS OF STUDYING THE CLINICAL REACTION

FIRST LECTURE.*

BY THOMAS LEWIS.

UNIVERSITY COLLEGE HOSPITAL, LONDON, ENGLAND

Introductory and Historical. In this lecture and that which follows I propose to deal with the action of certain cinchona alkaloids upon the heart, with special reference to the clinical condition termed fibrillation of the auricle. The alkaloid claiming chief attention will be quinidine, though something will be said of two allied alkaloids, quinine and hydroquinidine.

The first lecture will be devoted to the clinical aspects of the problem; in so far as I shall record original observations I shall record the observations undertaken with my collaborators, Dr. A. M. Wedd, of Pittsburgh, and Dr. C. C. Iliescu, of Bucharest; the second will be devoted more to the experimental and theoretical aspects. This method of description is chosen not only because of its convenience, but also because we owe the remedy quinidine to clinical and not immediately to experimental methods of observation; its original discovery as a remedy for auricular fibrillation has been, so far as I am able to judge from published accounts, one of those happy accidents which at very rare intervals help the progress of medical knowledge. But this statement, if it is not to convey a wrong impression, needs to be qualified. That quinidine would have been discovered as a remedy for fibrillation of the auricles by unaided therapeutics is in high degree improbable. The time was ripe for the discovery; it was ripe because irregular action of the heart had been analyzed into its several distinct forms, forms named and recognized the world over.

* Based on work undertaken for the British Medical Research Council at University College Hospital Medical School, London. A Noble Wiley Jones Lecture delivered at the University of Oregon Medical School, Portland, in May, 1922. Second and third lectures will appear in the July and August issue of this publication.

Consider the frequency with which the human auricle is and has been affected by this disorder fibrillation; consider also the tens of thousands of patients who have received doses of cinchona alkaloids, adequate to produce the change from the disordered to the ordered rhythm, and it becomes inconceivable that this change had not happened many times before Wenckebach specifically drew attention to it. It is the more inconceivable since cinchona has for very many years obtained a vague but quite uncertain reputation as a cardiac tonic.

Given a profession still unable to differentiate between one form of irregularity and another, unable to distinguish between the pulse disordered by fibrillation and the pulse scarcely disturbed by slight changes of respiratory vagal tone, and that profession would have remained ignorant of the profound effects which quinidine exerts upon the heart in a special group of cases. It is when we consider the question historically, and from this aspect, that we are able to grasp, what I think it is important we should at once grasp, that this discovery was made possible only by experiment upon the hearts of lower animals and by the forthcoming analyses of clinical irregularities. The very fact that we owe these remedies primarily to Wenckebach, whose work in this analytical field is for all time classical, speaks for itself. Wenckebach¹¹ wrote of quinine. In two patients, the subjects of paroxysmal fibrillation, he observed beneficial effects to follow the administration of this alkaloid; it does not appear that Wenckebach gave this drug expecting an action antagonistic to fibrillation. He gave this and many other drugs having very diverse actions; only digitalis bodies and quinine, the latter in a very small proportion of the cases, showed beneficial action. The old and oft-repeated statements that cinchona is of value as a cardiac tonic brought no progress; unaided they could bring no progress. In 1914 Wenckebach discriminated. He named the drug as bringing fibrillation of the auricle to an end.

It was his stated wish for further trials in this specific direction that prompted von Frey's work⁷ in 1918. Von Frey used not only quinine, but also its isomer quinidine and other related alkaloids, and from him came the important statement, first, that quinidine is of this series the potent alkaloid, and, second, that it will abort not only short-lasting paroxysms but also long-continued fibrillation. Von Frey's statements were soon confirmed by von Bergmann¹ and by others.^{2 3} In the last two years favorable reports have begun to issue from many countries; in America through Levy;⁸ in my own country through Drury and Iliescu.⁵

Fully to appreciate this discovery, our conclusions in respect of fibrillation a few years ago are to be remembered. Generally recognized to be the commonest, or the only common grave disorder of the heart beat, it was known to display itself in two forms:

in the form of short paroxysms, lasting a few hours or a few days, and much more often as a malady persisting until death. The view was held that if auricular fibrillation had lasted ten days, it was a settled thing. There were, it is true, a few very isolated cases (like that of Lea⁸) where it passed away after lasting a longer time; but the statement still holds that once established for a few weeks, the prospect of its spontaneous passage is beyond reasonable expectation.

Consider briefly its effects: It paralyses the action of the auricles, it wholly abolishes the regularity of the natural pulse, two effects, each of which hampers the circulation in some measure; but it has a third and more malign influence, it lifts the rate of the beating ventricle. The average rate in man at rest is 70 to the minute, in the disordered state the average and uninfluenced rate at rest is about 90 to 100 beats per minute. In quiet walking exercise the normal rate may be 80 or 90 to the minute; in fibrillation the corresponding figures are roughly speaking 130 to 150 to the minute. It is the uncontrolled state of the heart in exercise which constitutes the most serious feature of fibrillation. Thus, fibrillation throws upon the heart a greatly increased burden, a burden which the weakly heart often finds beyond endurance. Because fibrillation of the auricles so upsets the balance between the calls to work and the power to work, because failure with congestion so often follows in its train, it has come rightly to be regarded as one of the outstanding phenomena of cardiovascular maladies. It is upon this condition that quinidine exerts its beneficial action, restoring the normal rhythm to hearts which have beat irregularly for months or years. The drug as now usually administered is given in repeated doses of 0.2 to 0.4 gm. the allowance being from 1 to 2 gms. per diem. The change may come on the first day, it may be delayed for several or many days; but it can be produced in about 50 per cent of all cases so treated. To the question of dosage I shall return in more detail; meanwhile it will be convenient to study the clinical effects more closely; and in doing so I shall first describe methods of observation recently introduced.

Method of Investigation. The change from auricular fibrillation to normal rhythm may be recognized by those familiar with the disordered heart action without the aid of instruments; the same event may be recorded graphically by the polygraph. The electrocardiograph, as usually employed, gives further information. It provides a general notion of the events which are happening in the auricle which is coming under the influence of quinidine, events premonitory to the actual change of mechanism. A fall in the rate of the auricular oscillations and an occasional intermediate phase of "flutter" have been reported by von Frey, who used this method. But electrocardiography as generally employed is not so suitable as a method recently introduced. To study the effects of quinidine

upon the fibrillating auricles the oscillations must be recorded in as pure a form as possible; this is not accomplished by leading from the limbs, for the curves are then complicated by fine movements in the corresponding somatic muscles, but by leading directly from the chest wall in the neighborhood of the right auricle, as Drury and Iliescu have shown.⁴ This method was first used by Drury and Iliescu⁵ in studying the action of quinidine upon the auricle, and has now become the routine practice of my laboratory. By means of this near lead, records can be obtained of the oscillations in a sufficiently pure form to permit of counting, without the introduction of material error. The records give an accurate measure of ventricular rate and its variation, and a sufficiently accurate measure of auricular rate and its change.

The rate of the main auricular oscillations, those which correspond to the circus movements, in clinical fibrillation averages 450 per minute; the actual rates for individual cases are usually near this average rate, but in occasional cases the rate may be as high as 620, or it may be as low as 380 per minute. For any given case the rate of oscillation is remarkably constant over long periods, providing that uniform conditions of observation are maintained. So far as has yet been ascertained, conspicuous alterations of rate are produced only by the administration of certain drugs, though on relatively infrequent occasions there are changes of rate which are imperfectly understood. This constancy of rate under resting conditions has its value to us, for it permits us to obtain clearer pictures and comparisons of changes produced by drugs.

The Reaction and Dosage. *Single Doses.* Let us consider first the effects of single doses of quinidine; a dose such as 0.8 gm. of the pure dried base. Such a dose invariably induces a profound reaction, beginning usually half an hour after the drug is swallowed enclosed in a thin gelatine capsule. The auricular rate falls steeply and reaches its minimum usually in two hours after the drug's administration. But this minimum rate is not maintained; very soon recovery begins. This is slow, being spread over twenty-four to thirty hours. Eventually, it is complete, the original rate being reached. Fig. 1 typifies the auricular reaction. Meanwhile, as von Frey noticed, the ventricular rate has been raised; it rises simultaneously with the fall of auricular rate, rises steeply and recovers slowly. The total fall of auricular rate is of 150 or 200 beats per minute, the level reached being in the region of 300 beats or less per minute. The total rise of ventricular rate is variable, in some cases it is comparatively small, in others it is conspicuous and such rates as 140 or even 160 are reached. The recovery from quinidine is due to the drug's elimination by the kidneys. The alkaloid appears first about two hours after its administration and continues to be excreted for many hours in large quantity; traces may be found twenty-four hours after the

administration, but that is not the rule. These statements are based on qualitative tests with Mayer's reagent (mercuric iodide 13.546 gms; potassium iodide 49.8 gms. and a liter of distilled water). In an acid urine, containing the alkaloid, a dense white precipitate is formed by a drop of the reagent. (For further information on the output of cinchona alkaloids see Wiechmann.¹²)

The constancy of these reactions in a given patient may be displayed by repeating them, allowing a sufficient time for recovery to elapse between the doses.

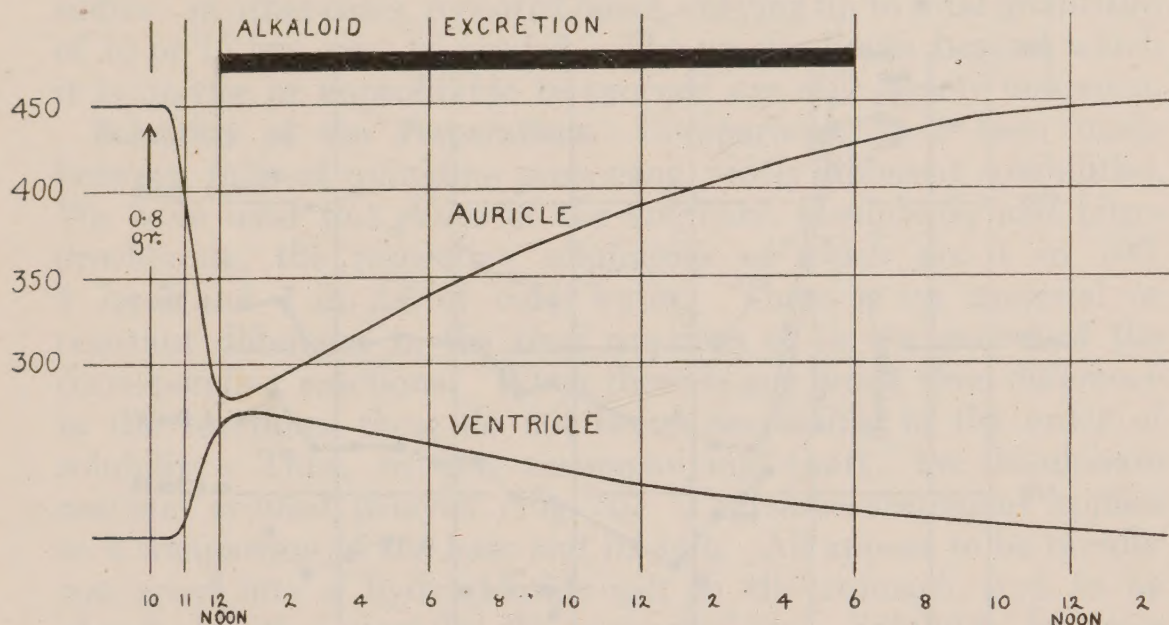


FIG. 1.—A diagram showing the change in auricular and ventricular rates which occurs when a single dose of 0.8 of a gram of quinidine is given by the mouth, in cases of auricular fibrillation. The rates of the auricle are shown to the left; the hours are shown below.

Increasing Doses. That the extent of the reaction depends upon the dose is easily proved by the administration of increasing doses at suitable intervals. Thus, if single doses of 0.2, 0.4 and 0.6 gm. are given on alternate days, the falls of auricular rate increase by approximately equal increments (Fig. 2); it is to be observed, however, that 0.4 gm. gives less than double the fall produced by 0.2 gm.; the falls begin from a common baseline, recovery being complete in the intervals between the doses.

Repeated Doses. But there is a limit to these regular reactions; an increased dose will not produce indefinitely a correspondingly increased fall. Such at all events seems to be the inference from observations of a slightly different type. If a single dose of 0.6 gm. is given and a second and like dose is administered at such a time that the fall produced by the second dose should begin when the reaction of the first dose is at its height, an equal second fall is not obtained; it is a fall of much less extent.

Similarly, if doses of 0.4 gm. are administered at intervals of three or four hours during the day, the initial fall of rate is rapid

and progressive; but there comes a time in many patients when the rate becomes stationary or almost so, falling a little at each dose and rising a little subsequently. To drive the auricular rate lower, an increase in quantity may be necessary, a dosage of, say, 0.6 gm. at four-hour intervals. Even so, stationary rates may be seen. There is a limit to the quantity which may be given safely at single doses, and the failure to obtain further slowing with high dosage is one of the reasons why, in using quinidine therapeutically, treatment has sometimes to be abandoned.

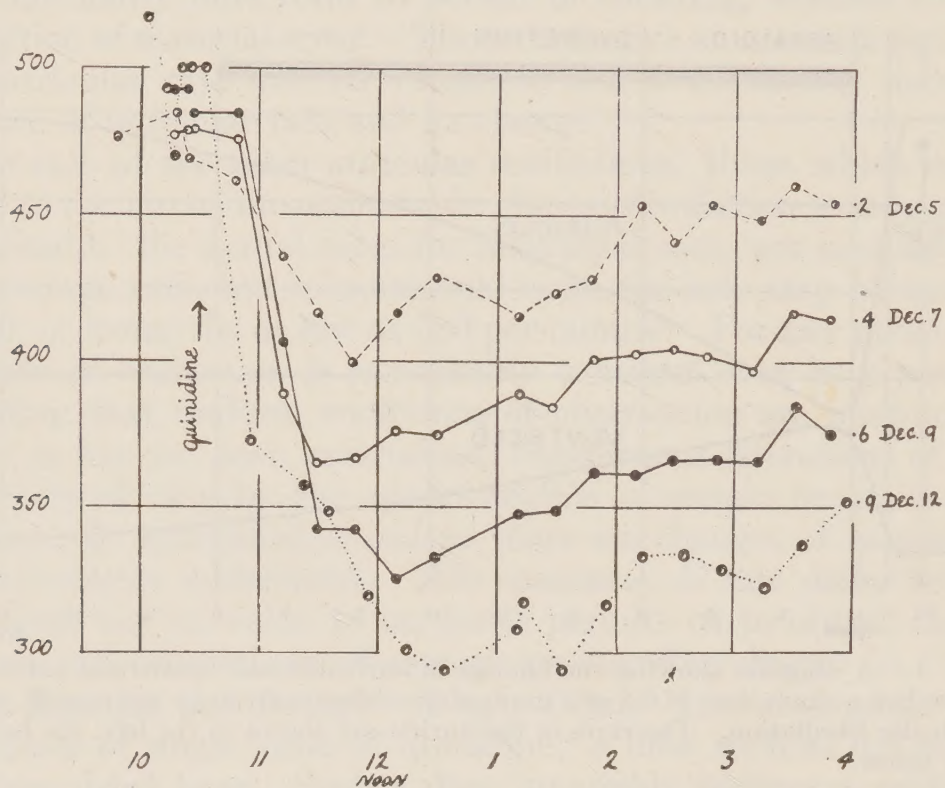


FIG. 2.—Four curves of auricular rate from a case of fibrillation of the auricles, comparing the effects of different doses of quinidine.

The desired result, a return of the normal heart rhythm, occurs after very variable quantities of the alkaloid have been administered. In some patients a single dose of 0.6 gm. produces a steep fall which ends in the abrupt cessation of fibrillation. Much more frequently the change is obtained by using repeated doses of 0.4 gm. given every three or four hours each day. The change comes, if it comes at all, usually when the auricular rate falls to such rates as 300 or 250 per minute. In giving repeated doses it is not always necessary to force the rate below such levels; maintenance of the rate at these levels often suffices, the change to normal rhythm coming unexpectedly at any time during the continuance of such treatment. But it is necessary to allow no escape from these rates. The resumption of the natural heart beat does not occur during the phase of recovery from quinidine. Recovery, as we have seen, occurs with some speed, owing to the quick elimination of the alkaloid; as Drury and Iliescu have pointed out, if three or four

doses of 0.4 gm. are given in the day, the rate will fall progressively for that day; but the curves obtained next morning show already that the effects of the drug are rapidly subsiding; the next day's treatment therefore does not start from the last night's level, there is some leeway to make up. To counteract this loss to the reaction one or more similar doses may be given during the late hours of night or early morning. Clearly, the actual doses and times of administration are best controlled by studying the records obtained as treatment proceeds.

It has been said that a single dose of 0.6 gms. of the drug may suffice; in other cases, repeated doses, varying up to total quantities of 10 or 15 gm. may be needed. The precise limits beyond which it is unwise or unprofitable to proceed are still largely unknown.

Solubility of the Preparations. Comparisons have been made between salts of quinidine possessing widely different solubilities. We have used test doses of the sulphate, bisulphate, and bihydrochloride, the respective solubilities of which are 1 in 100, 1 in 7 and 1 in 3.6 of cold water. There is no material or constant difference in the time relations or in the extent of the corresponding reactions. When there is any small time difference in the reactions, these do not occur necessarily in the order of solubility. Thus, in the accompanying chart, the bisulphate reaction is most delayed (Fig. 3). The same statement applies to a comparison of the base and its salt. All appear to be rapidly converted into a hydrochloride salt in the stomach, and to be absorbed with essentially the same rapidity. Solubility becomes therefore a question purely for convenience in prescription, where it is desired to give the drugs in fluid form; it is actually our practice to give the drug in thin gelatine capsules.

Reaction to Allied Alkaloids. Only two of the allied alkaloids will be discussed at the present time. Quinine, the alkaloid first used by Wenkebach, was reported by von Frey to be less potent than quinidine, and other writers, though not all, have agreed with him. The reason for disagreement probably is twofold: (1) Commercial preparations of the alkaloid often contain very large percentages of impurities and these impurities influence the result; (2) the potency of an alkaloid is gauged by the quantity needed to restore the normal rhythm. Now this quantity varies, not only with different alkaloids but with the same alkaloid, and with the same alkaloid administered to one and the same case. Consequently, comparisons of potency undertaken by the method which has been used are uncertain, and they must remain so unless large numbers of cases are treated alternatively with the two alkaloids to be compared.

There is a quicker method, that which we have recently employed, namely, the use of fixed test doses and a comparison of the falls of auricular rate. Using this method we find that von Frey's

statement is true. Quinidine is weight for weight much more potent than quinine—the fall given by 0.6 or 0.8 gm. of the latter, as compared with that given by quinidine is often inappreciable and rarely amounts to one-fifth of that which follows a similar dose of quinidine. The same method of comparison has been

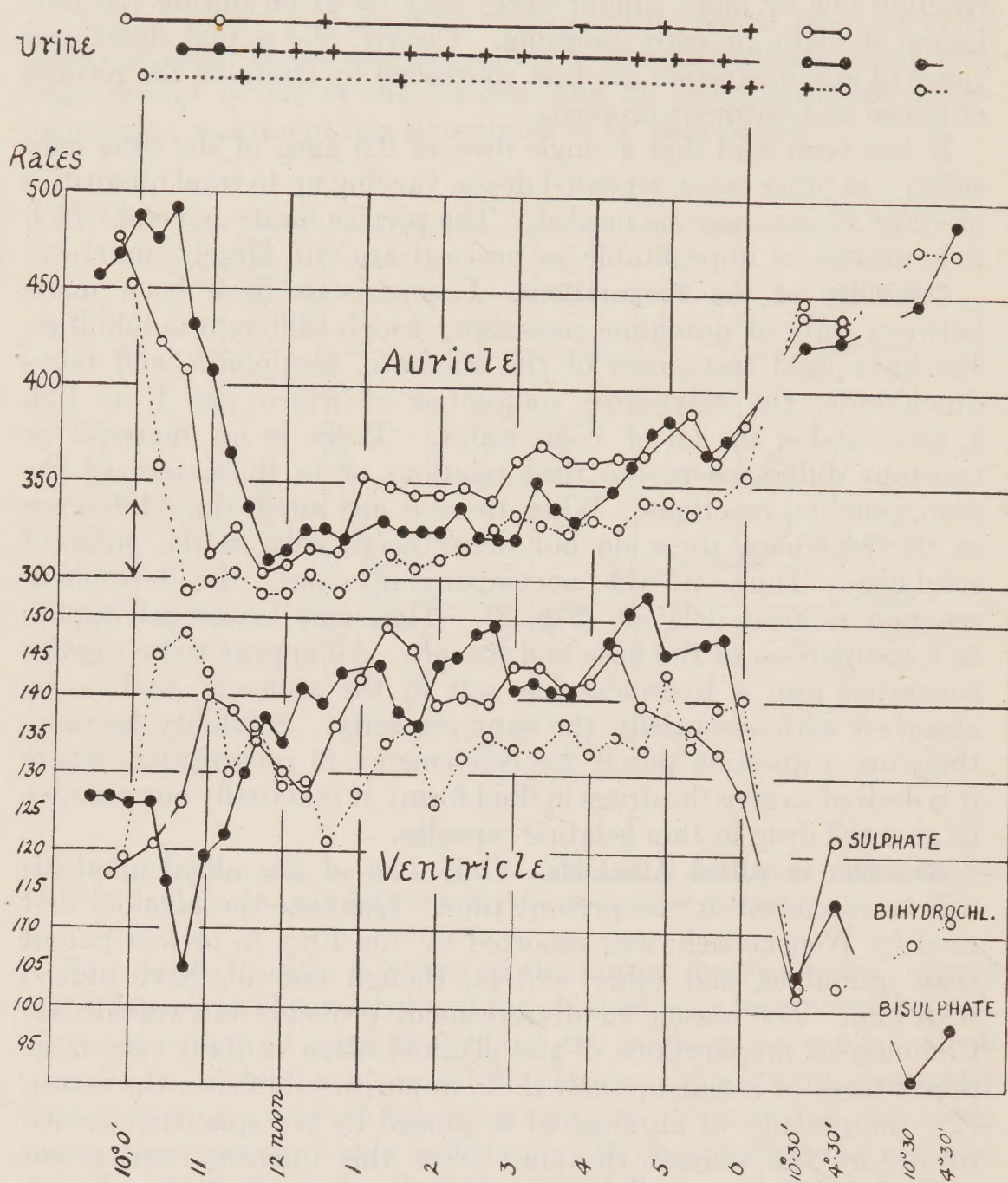


FIG. 3.—Curves of auricular and ventricular rate in a case of auricular fibrillation. The test dose of 0.8 of a gram of quinidine salt was given at 10 o'clock. Above the chart the presence of alkaloid in the urine is indicated by a + sign and its absence by a ° sign. The curves are broken where a night intervenes.

used in the case of hydroquinidine; this alkaloid has been tested because it is the chief alkaloid contaminating commercial quinidine preparations; to purify quinidine from hydroquinidine is not an easy matter and, so I am told, has but recently been accomplished with any considerable measure of success. A com-

parison of the action of the two alkaloids is therefore a matter of some consequence from the commercial standpoint. Actually, it is found that the two alkaloids have a very similar potency, hydroquinidine being if anything a little the more powerful (Fig. 4).

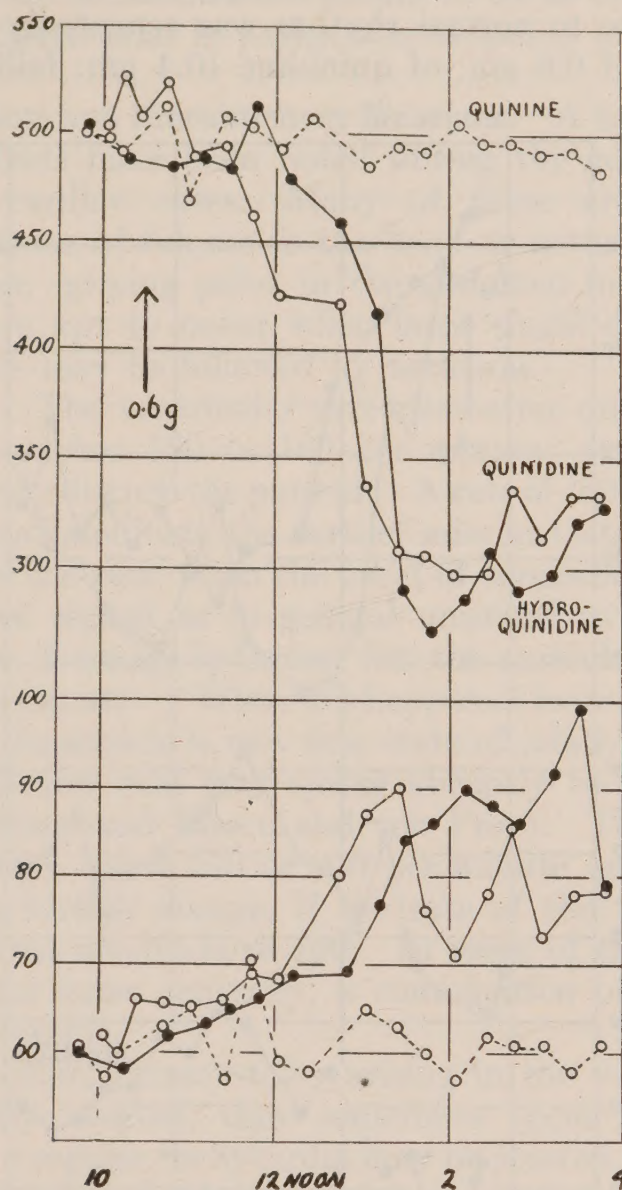


FIG. 4.—A similar chart, comparing the effects of separate test doses (0.6 of a gram) of quinidine, quinone and bihydroquinidine. •Auricular curves above and ventricular curves below.

Simultaneous Digitalis Therapy. It has been stated on more than one occasion that digitalis interferes with the reaction to quinidine and that the two drugs should not be given simultaneously. Comparisons of the fall of auricular rate obtained by quinidine, before and after the administration of digitalis in full therapeutic doses, usually show but small differences. The original auricular rate is generally speaking a little higher when the heart is under digitalis; the fall in quinidine is usually as great (Fig. 5) or almost as great, though it does not usually reach quite so low a level when digitalis has been given; in some comparisons, too, the fall of rate

has appeared to be delayed by digitalis (Fig. 5); in others a more decided lessening of the fall has been noticed. A striking difference in the two reactions is not the rule; such differences as exist do not seem often to be of consequence, and we think that the antagonistic action of digitalis has been exaggerated. In one patient in whom a change to normal rhythm was repeatedly obtained with a single dose of 0.6 gm. of quinidine (0.4 gm. failing to produce

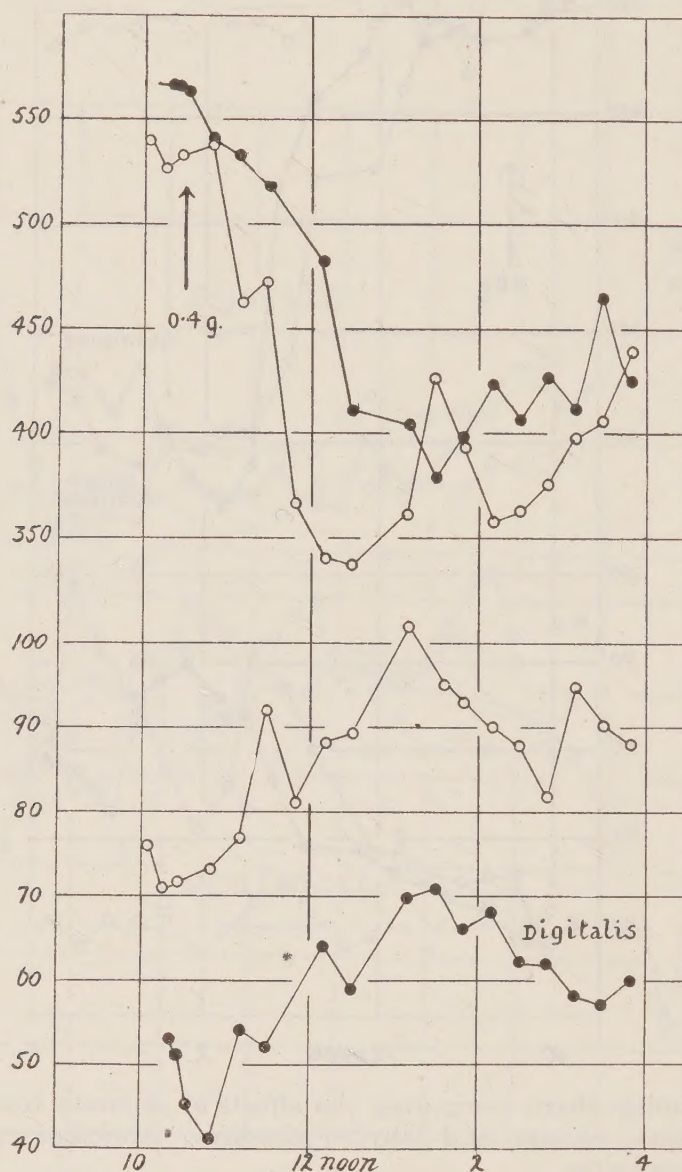


FIG. 5.—A similar chart, comparing the effect of a single test dose (0.4 of a gram) of quinidine, given to a patient before (plain circles) and after (black circles) the administration of nine drams of tincture of digitalis in eleven days.

the transition), the same dose was effective after the patient had been fully digitalized. Now the simultaneous administration of digitalis has a great advantage, for it keeps the ventricular rate at a comparatively low level throughout the quinidine reaction (Fig. 5) and one source of trouble is thereby removed. A course of digitalis immediately preceding the use of quinidine, or a lighter course actually simultaneous with the quinidine, seems often to

be indicated rather than contraindicated; it may be necessary to give rather heavier doses of quinidine in these circumstances, but the control of ventricular rate is in many patients a factor of advantage with which we can hardly afford to dispense. At all events the simultaneous administration seems to us to deserve a further and more extended trial in patients predisposed to give high ventricular rates.

Adverse Effects and Precautionary Measures. A number of undesired toxic effects have been noted during the administration of quinidine in cardiac cases. Many of these are unimportant. Giddiness, a sense of fulness in the head or actual headache, are not uncommon; griping pains in the abdomen followed by loose evacuations are apt to occur when large single doses are given. Repeated doses may be followed by urticaria.

Palpitation. The ventricular rate rises after quinidine and not uncommonly reaches 120 to 160 per minute; it is part of the reaction and may disturb the patient. A rate of 160 would no doubt on occasion contraindicate the further administration of the drug. That would be the case when the onset of congestion threatened—cases which we regard as in general unsuited to the treatment. In a few cases, if dosage is carried far, the auricular rate may fall toward 200 per minute. When this happens a more serious accident may happen: the auricle is now in a state of relatively pure flutter and the ventricular rate may spring abruptly to the full rate of the auricle (Drury and Iliescu and von Frey). The development of auricular rates below 250 or 240 per minute appears to me to contraindicate further dosage, if the rate of the ventricular rate has already risen much above 100. In cases of this kind, and of high ventricular rates generally, a combination of quinidine and digitalis is preferable.

Under quinidine, extrasystoles arising in the ventricle are frequent. Usually isolated, they sometimes occur in groups, and in a few cases a regular tachycardia may be started in the ventricle. The precise meaning of this interesting phenomenon is not known, but tachycardia of ventricular origin is so closely allied to graver disorders of the ventricle, that the appearance of multiple extrasystoles should be a signal to cease the administration of quinidine.

Idiosyncrasy to Quinidine. Some few patients exhibit a serious intolerance of quinidine. Of these I have no personal experience, but von Frey has reported cases in which after a small dose of quinidine sudden loss of consciousness with standstill of respiration has happened. Recovery occurred in his cases, but it is clear from his account that the condition is a very serious one. It is from this experience that the custom has arisen of giving first a small trial dose of 0.2 gm., following this after twenty-four hours by a single dose of 0.4 gm. The treatment is begun on a subsequent day. Whether this method of small trial doses will eliminate danger

from this source remains for the future to decide. It is to be remarked that accidents of the kind are rare.

Dangers of Embolism. Many years ago I witnessed for the first time a curious and fatal accident. It occurred in a woman suffering from mitral stenosis and heart failure.¹⁰ This woman acquired an attack of fibrillation of the auricles which lasted for several days and then suddenly ended; when it ended clots were detached from the heart, which produced multiple embolism of the lungs and brain, and these led quickly to a fatal termination. Fibrillation of the auricles predisposes to clotting in the auricular appendices. Antemortem thrombi are found in patients dying of heart failure more frequently if the auricles were fibrillating at the time of death. Thus in 76 postmortems on cases dying of chronic heart disease, in which clots were specially sought, I found them in 8 cases out of 23 in which fibrillation was present in the last illness and in only 4 cases out of 53 in which the mechanism had been normal. But embolism due to detachment of these clots does not appear to be more common when fibrillation exists than when the action is normal. While fibrillation predisposes to clotting, the normal auricular action favors the detachment of such clots. In treating patients with quinidine these facts should be born in mind; because we have borne them in mind we have seen no instance in which the resumption of the normal rhythm under quinidine has led to embolism; others have been less fortunate.

When there is much dilatation of the heart, as indicated by congestion of the veins and liver, the therapeutic use of quinidine is contraindicated. In cases in which there have been symptoms or signs of recent embolism, the use of the drug invites disaster. From embolism there is not much to fear providing those chosen for treatment are judiciously selected; but it is to be observed that the peril of embolism precludes the use of quinidine in cases of fibrillation in which the circulation is embarrassed. It sets another limit to its usefulness.

In paroxysmal fibrillation, a fear of embolism should not deter us from giving quinidine. The paroxysm will cease spontaneously after awhile, and clotting is the more likely to occur the longer the attack lasts. Theoretically, if quinidine will bring the attack more speedily to a close, the chances of clotting and subsequent embolism will be diminished.

The Therapeutic Value of Quinidine. The percentage of cases in which quinidine, as it is used at the present time, will restore the normal rhythm in the fibrillating auricles is approximately 50 per cent. With these figures, drawn from previous records, the experience of my own clinic agrees. The figure applies to chronic fibrillation of the auricles.

When in a case of auricular fibrillation the normal rhythm is restored, the gain to the patient is considerable. It is not so

apparent while the patient lies in bed, for in the cases most suitable for treatment there are few or no symptoms at rest. It is when the patient goes about again and undertakes his daily duties that he feels real benefit; and the benefit is chiefly due to the heart being once more under strict nervous control. In particular, exercise no longer raises the rate to levels which are incompatible with comfort or which produce actual distress. The change brings similar benefits to the heart as does the lowering of ventricular rate by digitalis; quinidine has the advantage however, in patients in whom its effects are permanent, in that it frees them from further drug treatment. In treatment by digitalis the drug has to be maintained, in most cases indefinitely.

Nevertheless, the usefulness of the drug from the clinical standpoint is limited. It is limited by the high percentage of failures (50 per cent) to restore the normal rhythm. Too much emphasis should not be laid upon these failures however, for it seems probable that the percentage will be reduced as further experience is gathered.

It is limited also by its unsuitability in cases of venous stasis. But the chief limitation is more serious and consists in the early and very frequent resumption of auricular fibrillation. In not a few patients the restored normal rhythm lasts but a few days or a week, and fibrillation returns again and again after successive periods of treatment. In others the normal rhythm is maintained for a few weeks or months; a few cases have been observed in which it has been maintained for six months or a year. In the last group it must be judged an unqualified success, but in proportion as from case to case the return of fibrillation is less delayed, so the remedy becomes less practicable as a remedy. The value of quinidine has so far been greater in adding to our knowledge of fibrillation of the auricles than it has been in therapeutics. It has taught us many important facts, and among the most notable is that the hearts which display chronic auricular fibrillation are *capable* of beating normally, a quality hitherto in doubt. It has also taught us that the cause which predisposes to fibrillation, or at first initiates fibrillation, is maintained in the chronic state. Although it seems clear both from experimental and clinical observation that fibrillation once established tends to maintain itself, it is no longer possible to accept the conclusion that once established it will perpetuate itself indefinitely, though its original cause is removed. The pronounced tendency for the disorder to recur is opposed to any such conclusion; it teaches us that we have still to seek the ultimate causes of the disorder and that the prospect of fully successful treatment is along those lines of investigation.

As in our early publications, my collaborators and myself still deprecate the general use of the drug. At the present stage of

investigation it should be employed only under strictly controlled conditions; it is a treatment emphatically for the wards rather than for use in an outpatient department.

REFERENCES.

1. Bergmann: Münch. med. Wchnschr., 1919, **66**, 705.
2. Boch: Mediz. Klinik, 1921, **17**, 1052.
3. Boden and Neukirch: Deutsch. Arch. f. klin. Med., 1921, **136**, 181.
4. Drury and Iliescu: Heart, 1921, **8**, 171.
5. Drury and Iliescu: British Med. Jour., 1921, **2**, 511.
6. Ellis and Kennedy: Lancet, 1921, **2**.
7. Frey: Berl. klin. Wchnschr., 1918, **1**, 450 and 849; Deutsch. Archiv f. klin. Med., 1921, **136**, 70.
8. Lea: Heart, 1918-20, **7**, 47.
9. Levy: Jour. Am. Med. Assn., 1921, **76**, 289.
10. Lewis: "Clinical Disorders of the Heart Beat," 1916 (3d edit.), p. 95.
11. Wenckebach: "Die unregelmässige Herztätigkeit," etc., 1914, pp. 125 and 128.
12. Wiechmann: Ztschr. f. d. ges. exper. Med., 1919, **7**, 155.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

GEORGE MORRIS PIERSOL, M.D., Editor

JOHN H. MUSSER, JR., M.D., Assistant Editor

Monthly. Illustrated. 1920 pages yearly. Price, \$6.00 per annum

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, founded in 1820, has long been recognized as the leading medical journal of the English-speaking race. From the first it sought the epoch-making papers, and becoming recognized as their medium, it has, in turn, been sought by those who have had discoveries or real advances in the art and science of medicine to announce in its Department of Original Articles. During 1921 *The American Journal* will still further develop a feature that has proved most useful and popular, namely, a series of Special Articles, written by prearrangement with men of the highest authority, and covering present-day topics of the greatest importance and interest. These articles are designed to be clinical and practical, and to present important advances and the latest knowledge clearly and concisely, with particular reference to application in daily work. The Department of Book Reviews will continue to comprise critical and discriminating estimates of important new books, as well as briefer notices of books of less importance and of new editions. The Department of Progress of Medical Science, under the charge of recognized specialists, will continue to summarize the actual advances in the art and science of medicine appearing in the leading medical periodicals of the world.

PROGRESSIVE MEDICINE

**A Quarterly Digest of Advances, Discoveries and Improvements
in the Medical and Surgical Sciences, Covering the
Entire Domain of Medicine.**

Edited by HOBART AMORY HARE, M.D., Professor of Therapeutics, Materia Medica and Diagnosis in Jefferson Medical College, Philadelphia, etc. Assisted by LEIGHTON F. APPLEMAN, M.D., Instructor in Therapeutics, Jefferson Medical College, Philadelphia. In four octavo volumes, containing 1200 pages, amply illustrated. Annual subscription price, cloth binding, \$11.00, *net*.

PROGRESSIVE MEDICINE is the story of the progress, discoveries and improvements in the various branches of the medical and surgical sciences, and is published four times a year, in March, June, September and December. The matter presented is the digested essence of the entire medical literature of the world published during the previous twelve months, modified, explained and criticised in the light of the personal experience of the contributor. By this method useless information is discarded and only that which is valuable and really helpful to the practitioner is retained. Practicality and thoroughness are the controlling features. The contributors are authorities in their respective lines, and their experience in private and hospital practice enables them to choose unerringly that which their brother workers require. Every article is original, the veritable product of the author whose name it bears. The style is narrative in form, hence easy to read. The interpretation of the facts stated is given and their bearing upon the whole subject under consideration is clearly and simply indicated.

706-10 Sansom St. **LEA & FEBIGER** PHILADELPHIA